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学位論文名	Elucidation of the etiopathology of autoimmune diseases using DNA microarray and bioinformatics analysis （DNAマイクロアレイとバイオインフォマティクスを用いた自己免疫疾患の病因・病態解明）
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論文内容の要旨

Introduction: Recent genome-wide association studies have advanced our understanding of genetic factors that underlie some of the autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Despite extensive efforts aimed at elucidating the cellular and biological abnormalities that arise in the immune system of patients with autoimmune diseases, the pathogenesis of these autoimmune diseases remain unclear. These diseases also have an environmental component, which can trigger or exacerbate the disease condition. Both genetic backgrounds and environmental factors may affect gene expression profile of patients with autoimmune diseases. I recently carried out gene expression profiling of peripheral blood cells (PBCs) from patients with SLE and bone marrow cells (BMCs) from patients with RA followed by bioinformatics analysis, and discovered the existence of abnormal regulatory networks and potential key molecules in the aberrant regulatory networks.

Methods: Gene expression profiles of PBCs from SLE patients and healthy individuals, or of BMCs from RA and osteoarthritis (OA) patients, were analyzed using DNA microarray analysis. Genes identified to be differentially expressed according to microarray analysis between SLE patients and healthy individuals, or between RA and OA patients, were functionally categorized using Expression Analysis Systematic Explorer (EASE) version 2.0 bioinformatics software. Interactions among the molecules of which the genes were differentially expressed in their respective gene categories were further investigated using Ingenuity Pathway Analysis. Cytokine interactions were also examined *in vitro*.

Results: Genes related to the immune response were differentially expressed in patients with SLE compared to healthy individuals. Increased expression of interferon (IFN)-inducible genes (*i.e.*, the "IFN signature") was confirmed in PBCs from patients with SLE. The results also suggested that TNF may repress the abnormal regulation by IFN-α in SLE while IFN-γ may have synergistic effect. Interactions between IFN-α and one of TNF, IFN-γ, or E2 appear to be involved in the pathogenesis of SLE. Given that SLE is a systemic disease that influences multiple organs, it is also importance to assess biological and cellular abnormalities associated with SLE other than those related to the immune response. To this end, I revealed that, in addition to the upregulation of apoptosis-related genes, genes related to sensory perception and response to radiation/light were downregulated. Functional abnormalities of ATP synthesis and DNA repair were implicated in peripheral blood cells from patients with SLE. Similar IFN signature was also observed in BMCs from RA but not in PBCs. Furthermore, HLA-E, G, F which are typical MHC class I molecules, were overexpressed in the BMCs from RA patients. Abnormal regulatory networks in the immune response identified in BMCs from RA patients, indicate that the bone marrow is pathologically involved in RA.

Conclusions: Similar aberrant cytokine regulatory networks were found in both SLE and RA. Whereas IFN signature was observed in PBCs of SLE, the similar IFN signature was found in BMCs but not in PBCs of RA. Although SLE and RA are the two different autoimmune diseases, this similarity may suggest a common autoimmune mechanism occurred in these diseases. These results do provide an additional layer of insight for the pathogenesis of SLE and RA.

論文審査の結果の要旨

代表的な自己免疫疾患である、全身性エリテマトーデス（SLE）と関節リウマチ(RA)患者の末梢血ならびに骨髄細胞における遺伝子発現を、DNAマイクロアレイを用いて網羅的に解析し、さらにバイオインフォマティクスを利用して、細胞機能の異常について検討した。

SLE患者の免疫機能は亢進しており、Type I インターフェロン（IFN）とType II IFN、TNF、エストラジオールが互いにネットワークを形成しながら病態に関与する可能性を示した。また、アポトーシスと光刺激反応にも機能異常を見出した。特に、ミトコンドリアDNAにコードされた遺伝子とATP依存性DNA修復遺伝子の発現低下を見出し、これらはSLEの病態形成に重要な役割を果たしている可能性がある。また、RA患者の骨髄でもSLEと類似のIFNを中心とする免疫機能の活性化状態が見出された。これらの自己免疫疾患の研究へのバイオインフォマティクスの応用は独創的であり、更なる発展性が期待できる。よって、博士（生命機能）の学位に値する。